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ORIGINAL ARTICLE

Ischaemic cardiovascular risk and prescription of non-steroidal anti-inflammatory drugs for musculoskeletal complaints

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Abstract

Objective. To determine the influence of ischaemic cardiovascular (CV) risk on prescription of non-steroidal anti-inflammatory drugs (NSAIDs) by general practitioners (GPs) in patients with musculoskeletal complaints. **Design.** Cohort study. **Setting.** A healthcare database containing the electronic GP medical records of over one million patients throughout the Netherlands. **Patients.** A total of 474 201 adults consulting their GP with a new musculoskeletal complaint between 2000 and 2010. Patients were considered at high CV risk if they had a history of myocardial infarction, angina pectoris, stroke, transient ischaemic attack, or peripheral arterial disease, and at low CV risk if they had no CV risk factors. **Main outcome measures.** Frequency of prescription of non-selective (ns)NSAIDs and selective cyclooxygenase-2 inhibitors (coxibs). **Results.** Overall, 24.4% of patients were prescribed an nsNSAID and 1.4% a coxib. Of the 41,483 patients with a high CV risk, 19.9% received an nsNSAID and 2.2% a coxib. These patients were more likely to be prescribed a coxib than patients with a low CV risk (OR 1.9, 95% CI 1.8–2.0). Prescription of nsNSAIDs decreased over time in all risk groups and was lower in patients with a high CV risk than in patients with a low CV risk (OR 0.8, 95% CI 0.7–0.8). **Conclusion.** Overall, patients with a high CV risk were less likely to be prescribed an NSAID for musculoskeletal complaints than patients with a low CV risk. Nevertheless, one in five high CV risk patients received an NSAID, indicating that there is still room for improvement.

Key Words: Cardiovascular diseases, general practice, musculoskeletal diseases, non-steroidal anti-inflammatory agents, pharmacoepidemiology, The Netherlands

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of musculoskeletal (MSK) complaints because of their analgesic and anti-inflammatory properties. International and national guidelines on various MSK complaints, such as back pain, shoulder pain, and osteoarthritis, recommend prescribing NSAIDs, either as a first-choice analgesic

or as a second choice if paracetamol fails to provide sufficient pain relief [1–6]. The use of NSAIDs is known to be associated with peptic ulcer disease and its complications, most notably upper gastrointestinal (UGI) bleeding, obstruction, and perforation [7,8]. The need to limit these UGI complications led to the development of selective cyclooxygenase-2 inhibitors (coxibs), which are associated with a significantly lower incidence of UGI complications

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International guidelines recommend avoiding the prescription of NSAIDs in patients at high ischaemic cardiovascular risk. In this study, we found that:

- NSAIDs are prescribed in one in five patients with a high cardiovascular risk.
- Prescription of coxibs is higher in patients with a high cardiovascular risk than in those with a low cardiovascular risk.
- NSAID prescription decreased over time in all risk groups, but it appears that general practitioners do not fully consider the cardiovascular risks associated with NSAID use, indicating that there is room for improvement.

when compared with traditional, non-selective NSAIDs (nsNSAIDs) [9–12].

However, shortly after the introduction of coxibs, concerns were raised regarding their cardiovascular (CV) safety profile. In September 2004, rofecoxib was withdrawn from world markets after a randomized controlled trial showed the incidence of stroke, myocardial infarction, or sudden cardiac death in patients taking rofecoxib was twice that of patients taking a placebo [13]. An increased risk of ischaemic CV events was also observed in studies of other coxibs, leading the European Medicines Agency to contraindicate the use of any coxib in patients with established ischaemic heart disease, stroke or peripheral arterial disease in 2005 [14]. Since then, there is increasing evidence that the risk of ischaemic CV events is increased not only by the use of coxibs but also by the use of nsNSAIDs, with the possible exception of naproxen [15–18]. Recent guidelines and consensus therefore recommend avoiding the prescription of NSAIDs in general in patients at high CV risk [19–21].

In this population-based cohort study, we aimed to examine the association between ischaemic CV risk and the prescription of NSAIDs in patients with MSK complaints. In addition, we aimed to determine the influence of demographic factors, prior NSAID prescription, the type of MSK complaint presented and the presence of UGI risk factors and renal insufficiency on NSAID prescription in this group of patients.

Material and methods

Setting

A cohort study was conducted in the Integrated Primary Care Information (IPCI) database. This

primary health care database contains the electronic patient records of over one million patients registered with GPs throughout the Netherlands. In the Netherlands, all 16.8 million citizens are registered with a GP, who forms the first point of care and acts as a gatekeeper in a two-way exchange of information with secondary care. The electronic medical record of each patient can therefore be assumed to contain all relevant medical information, including medical findings and diagnoses from secondary care. Further details of the database have been described elsewhere [22,23].

Study cohort

The study population comprised all patients ≥ 18 years of age newly diagnosed with a MSK complaint between 1 January 2000 and 31 December 2010. Diagnoses were considered new if the patient had not been diagnosed with the same MSK complaint in the six months prior to consultation. Only patients with at least 12 months of valid database history prior to study entry were included. Diagnoses of MSK complaints were identified based on International Classification for Primary Care (ICPC) coding [24]. If the patient consulted his/her GP again with the same complaint within six months of initial diagnosis, this consultation was considered part of the same MSK complaint episode. For each patient, only the first newly diagnosed complaint episode was included. The date of first consultation was considered the index date.

Cardiovascular risk, upper gastrointestinal risk, and renal insufficiency

In defining CV risk, UGI risk, and renal insufficiency we aimed to conform to Dutch prescription guidelines as much as possible. For cardiovascular risk, no Dutch guideline is currently available, but a national consensus report was published in 2009 containing prescription recommendations [21]. In line with this report, patients were considered at high CV risk if they had a history of myocardial infarction, angina pectoris, stroke, transient ischaemic attack, or peripheral arterial disease prior to the index date. They were considered at moderate CV risk if they did not have one of the risk factors described above but did have a history of diabetes, hypertension, or hyperlipidaemia. Patients without any of these CV risk factors were considered at low CV risk. In addition, risk factors for the occurrence of UGI complications were identified. Based on the most recent Dutch guideline on the prescription of NSAIDs [25], patients were considered at high UGI risk if they had a history of upper gastrointestinal bleeding or ulceration, were

aged over 70 years or had two or more of the following risk factors: age 60–70 years, history of heart failure, diabetes, or severe rheumatoid arthritis, use of antithrombotics, corticosteroids, or selective serotonin reuptake inhibitors. They were considered at moderate UGI risk if only one of the latter risk factors was present. In the absence of any of these risk factors patients were considered to have a low UGI risk. Finally, we identified each patient's most recent available laboratory measurement of glomerular filtration rate (GFR) prior to the index date. If this GFR was < 30 mL/min, patients were considered to have significant renal insufficiency [26].

The history of the diseases and conditions described above were assessed based on ICPC coding and free text search strings. In the case of diabetes and hyperlipidaemia, the use of respectively antidiabetic and lipid-modifying drugs, identified based on ATC classification code [27], was taken into account in addition to ICPC coding as proxy. If patients had a history of rheumatoid arthritis based on an ICPC code L88, this was defined as being severe if they also had a prescription in the year prior to the index date of specific antirheumatic agents, immunosuppressants, hydroxychloroquine, sulfasalazine, or cyclophosphamide.

NSAID prescription

For all included patients, the first NSAID prescription issued during the complaint episode was identified based on ATC classification code [27]. Only NSAID prescriptions issued on the day of a consultation for the MSK complaint were included. It has been suggested that the use of naproxen is less likely to increase cardiovascular risk than the use of other nsNSAIDs, and that the prescription of naproxen may be warranted in patients at a high CV risk [19,20,28]. In addition, there are indications that the risk of CV disease increases with NSAID use in a dose-dependent manner [29]. To examine whether GPs take these possibilities into account, a sensitivity analysis was conducted excluding naproxen and excluding all low-dosed nsNSAID and low-dosed coxib prescriptions, which was defined as a prescribed daily dosage (PDD) smaller than half the defined daily dosage (DDD).

Statistics

Baseline characteristics of the moderate and high CV risk groups were compared with those of the low CV risk group using a chi-squared test for dichotomous variables and independent t-test for age as a continuous variable. Univariate analyses of potential predictors of NSAID prescription such as

age, gender, CV risk, and UGI risk were conducted and unadjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by performing logistic regression analyses. For the predictor CV risk group, the same univariate logistic regression analyses were performed stratified per UGI risk group. For this stratified analysis, we also conducted multivariate analyses to present ORs adjusted for other predictors of nsNSAID and coxib prescription. Finally, the influence of CV risk on coxib and nsNSAID prescription was studied stratified per time period, and ORs adjusted for the year of the MSK complaint episode within each time period were calculated, again using multivariate logistic regression analysis. All analyses were performed using SPSS version 20 (SPSS, Chicago, IL).

Study approval

The study was approved by the Board of Directors of the IPCI database.

Results

Study cohort

Between 2000 and 2010, 804 261 adult patients aged over 18 years contributed data to the IPCI database. These patients were comparable to the general population of the Netherlands with regard to age and gender (mean age 40 years, 52% female versus 41 years, 51% female in the Dutch general population) [30]. Of these, 474 201 patients (59%) presented with a new MSK complaint and were included in the cohort. Baseline characteristics of all included patients are described in Table I. This table also shows the baseline characteristics per CV risk group. When comparing patients with a moderate or high CV risk with those with a low CV risk, statistically significant differences were found for almost all characteristics with the exception of two symptomatic diagnoses of the MSK system.

Predictors of nsNSAID and coxib prescription

In total, 115 713 (24.7%) of all MSK complaint episodes were treated with an nsNSAID and 6456 (1.4%) were treated with a coxib (Table II). The most frequently prescribed nsNSAIDs were diclofenac, naproxen, and ibuprofen (respectively 58%, 13%, and 12% of all nsNSAIDs prescribed) and the most frequently prescribed coxibs were rofecoxib and etoricoxib (49% and 33% of all coxibs prescribed, results not shown in table).

Table I. Baseline characteristics in the study population.

	Total (n = 474 201) n (%)	Per CV risk group		
		Low CV risk (n = 365 534) n (%)	Moderate CV risk (n = 67 184) n (%)	High CV risk (n = 41 483) n (%)
Age (mean \pm SD)	46.6 \pm 17.4	42.2 \pm 15.5	58.9 \pm 14.7	65.3 \pm 14.5
Age category:				
18–35 years	144 797 (30.5)	138 809 (38.0)	4 532 (6.7)	1 456 (3.5)
36–50 years	147 497 (31.1)	127 403 (34.9)	14 773 (22.0)	5 321 (12.8)
51–65 years	108 132 (22.8)	69 526 (19.0)	25 735 (38.3)	12 871 (31.0)
> 65 years	73 775 (15.6)	29 796 (8.2)	22 144 (33.0)	21 835 (52.6)
Female	256 015 (54.0)	196 550 (53.8)	38 906 (57.9)	20 559 (49.6)
NSAID prescription in six months prior to diagnosis	37 637 (7.9)	26 472 (7.2)	6 831 (10.2)	4 334 (10.4)
MSK complaint episode:				
Symptomatic diagnosis				
Back/neck	108 213 (22.8)	86 957 (24.1)	12 641 (18.8)	7 615 (18.4)
Upper extremity	82 026 (17.3)	63 366 (17.3)	11 810 (17.6) ^{NS1}	6 850 (16.5)
Lower extremity	66 107 (13.9)	49 802 (13.6)	10 003 (14.9)	6 302 (15.2)
Generalized/other	59 986 (12.6)	46 572 (12.7)	8 035 (12.0)	5 379 (13.0) ^{NS2}
Arthritis	21 529 (4.5)	11 548 (3.2)	5 739 (8.5)	4 242 (10.2)
Inflammatory arthritis	4 676 (1.0)	2 874 (0.8)	1 045 (1.6)	757 (1.8)
Osteoarthritis	11 211 (2.4)	5 944 (1.6)	3 056 (4.5)	2 211 (5.3)
Gout	5 642 (1.2)	2 730 (0.7)	1 638 (2.4)	1 274 (3.1)
Radiculopathy	25 409 (5.4)	19 180 (5.2)	3 822 (5.7)	2 407 (5.8)
Trauma	55 211 (11.6)	45 586 (12.5)	6 064 (9.0)	3 561 (8.6)
Other	55 720 (11.8)	41 523 (11.4)	9 070 (13.5)	5 127 (12.4)
Individual CV risk factors: ³				
Diabetes	28 597 (6.0)	–	20 847 (31.0)	7 750 (18.7)
Hypertension	63 841 (13.5)	–	46 077 (68.6)	17 764 (42.8)
Hyperlipidaemia	30 600 (6.5)	–	18 129 (27.0)	12 471 (30.1)
MI/AP	27 118 (5.7)	–	–	27 118 (65.4)
Stroke/TIA	14 118 (3.0)	–	–	14 118 (34.0)
PAD	5 715 (1.2)	–	–	5 715 (13.8)
UGI risk group:				
Low UGI risk	335 556 (70.8)	305 168 (83.5)	22 003 (32.8)	8 385 (20.2)
Moderate UGI risk	63 843 (13.5)	34 692 (9.5)	21 058 (31.3)	8 093 (19.5)
High UGI risk	74 802 (15.8)	25 674 (7.0)	24 123 (35.9)	25 005 (60.3)
Renal insufficiency	285 (0.1)	27 (0.01)	118 (0.2)	140 (0.3)

Notes: CV: cardiovascular; NSAID: non-steroidal anti-inflammatory drug; NS: non-significant; MSK: musculoskeletal; MI: myocardial infarction; AP: angina pectoris; TIA: transient ischaemic attack; PAD: peripheral arterial disease; UGI: upper gastrointestinal. Comparisons were made for the moderate versus the low CV risk group and for the high versus the low CV risk group. All comparisons between moderate or high CV risk patients and low CV risk patients were statistically significant (p-value < 0.05), unless otherwise stated with the letters 'NS': non-significant. ¹Comparison with low CV risk patients not statistically significant, p-value 0.13. ²Comparison with low CV risk patients not statistically significant, p-value 0.19. ³Risk factors used to define low, moderate, and high CV risk groups.

Age, gender, and NSAID prescription in the six months prior to the index date were all predictive of nsNSAID and coxib prescription. The frequency of nsNSAID and coxib prescription also varied depending on the type of MSK complaint diagnosed. The prescription of coxibs was particularly high in patients suffering from arthritis. When corrected for age and gender, the odds of receiving a coxib were still ten-fold in patients with arthritis when compared with those with complaints after trauma (adjusted OR 9.8; 95% CI 8.4–11.5, not shown in table). The individual CV risk factors were all associated with a higher chance of coxib prescription and a lower chance of nsNSAID prescription. Similarly, patients

in the moderate and high CV risk group were significantly more likely to receive a coxib than patients in the low CV risk group. The pattern for prescription of nsNSAIDs was less clear, as they were prescribed somewhat more frequently to patients with a moderate CV risk when compared with those with a low CV risk, but less frequently to those with a high CV risk than those with a low CV risk. UGI risk was also a strong predictor of coxib prescription, whereas a high UGI risk was associated with a lower chance of nsNSAID prescription. Patients with renal insufficiency were less likely to be prescribed an nsNSAID and more likely to be prescribed a coxib than patients without renal insufficiency.

Table II. Predictors of prescription of nsNSAIDs and coxibs.

	No NSAID prescribed (n = 352 032) n (%) ¹	nsNSAID prescribed (n = 115 713) n (%) ¹	Coxib prescribed (n = 6 456) n (%) ¹	OR (95% CI)	
				nsNSAID vs. no NSAID	coxib vs. no NSAID
Age category:					
18–35 years	114 077 (78.8)	29 948 (20.7)	772 (0.5)	1 (ref.)	1 (ref.)
36–50 years	105 154 (71.3)	40 815 (27.7)	1 528 (1.0)	1.5 (1.5–1.5)	2.2 (2.0–2.3)
51–65 years	76 359 (70.6)	29 688 (27.5)	2 085 (1.9)	1.5 (1.5–1.5)	4.0 (3.7–4.4)
> 65 years	56 442 (76.5)	15 262 (20.7)	2 071 (2.8)	1.0 (1.0–1.1)	5.4 (5.0–5.9)
Gender:					
Male	159 766 (73.2)	55 909 (25.6)	2 511 (1.2)	1 (ref.)	1 (ref.)
Female	192 266 (75.1)	59 804 (23.4)	3 945 (1.5)	0.9 (0.9–0.9)	1.3 (1.2–1.4)
NSAID prescription in six months prior	24 860 (66.1)	11 688 (31.1)	1 089 (2.9)	1.5 (1.4–1.5)	2.7 (2.5–2.9)
MSK complaint:					
Trauma	49 345 (89.4)	5 605 (10.2)	261 (0.5)	1 (ref.)	1 (ref.)
Symptomatic diagnosis					
Back/neck	70 464 (65.1)	36 477 (33.7)	1 272 (1.2)	4.6 (4.4–4.7)	3.4 (3.0–3.9)
Upper extremity	56 150 (68.5)	24 558 (29.9)	1 318 (1.6)	3.9 (3.7–4.0)	4.4 (3.9–5.1)
Lower extremity	54 211 (82.0)	11 109 (16.8)	787 (1.2)	1.8 (1.7–1.9)	2.8 (2.4–3.2)
Generalized/other	46 926 (78.2)	12 308 (20.5)	752 (1.3)	2.3 (2.2–2.4)	3.0 (2.6–3.5)
Arthritis	13 943 (64.8)	6 545 (30.4)	1 041 (4.8)	4.1 (4.0–4.3)	14.1 (12.3–16.2)
Inflammatory arthritis	3 027 (64.7)	1 386 (29.6)	263 (5.6)	4.0 (3.8–4.3)	16.4 (13.8–19.6)
Osteoarthritis	8 239 (73.5)	2 349 (21.0)	623 (5.6)	2.5 (2.4–2.6)	14.3 (12.3–16.6)
Gout	2 677 (47.4)	2 810 (49.8)	155 (2.7)	9.2 (8.7–9.8)	10.9 (8.9–13.4)
Radiculopathy	16 699 (65.7)	8 269 (32.5)	441 (1.7)	4.4 (4.2–4.5)	5.0 (4.3–5.8)
Other	44 294 (79.5)	10 842 (19.5)	584 (1.0)	2.2 (2.1–2.2)	2.5 (2.2–2.9)
Individual CV risk factors:					
No CV risk factors	270 758 (74.1)	90 615 (24.8)	4 161 (1.1)	1 (ref.)	1 (ref.)
Diabetes	21 113 (73.8)	6 864 (24.0)	620 (2.2)	1.0 (1.0–1.0)	1.9 (1.8–2.1)
Hypertension	48 168 (75.6)	14 261 (22.4)	1 312 (2.0)	0.9 (0.9–0.9)	1.8 (1.7–1.9)
Hyperlipidaemia	23 118 (75.5)	6 853 (22.4)	629 (2.1)	0.9 (0.9–0.9)	1.8 (1.6–1.9)
MI/AP	21 113 (77.9)	5 356 (19.8)	649 (2.4)	0.8 (0.7–0.8)	2.0 (1.8–2.2)
Stroke/TIA	11 209 (79.4)	2 626 (18.6)	283 (2.0)	0.7 (0.7–0.7)	1.6 (1.5–1.9)
PAD	4 484 (78.5)	1 117 (19.5)	114 (2.0)	0.7 (0.7–0.8)	1.7 (1.4–2.0)
CV risk group:					
Low CV risk	270 758 (74.1)	90 615 (24.8)	4 161 (1.1)	1 (ref.)	1 (ref.)
Moderate CV risk	48 970 (72.9)	16 852 (25.1)	1 362 (2.0)	1.0 (1.0–1.1)	1.8 (1.7–1.9)
High CV risk	32 304 (77.9)	8 246 (19.9)	933 (2.2)	0.8 (0.7–0.8)	1.9 (1.8–2.0)
UGI risk group:					
Low UGI risk	248 705 (74.1)	83 753 (25.0)	3 098 (0.9)	1 (ref.)	1 (ref.)
Moderate UGI risk	45 724 (71.6)	16 792 (26.3)	1 327 (2.1)	1.1 (1.1–1.1)	2.3 (2.2–2.5)
High UGI risk	57 603 (77.0)	15 168 (20.3)	2 031 (2.7)	0.8 (0.8–0.8)	2.8 (2.7–3.0)
Renal insufficiency:					
No renal insufficiency	351 801 (74.2)	115 666 (24.4)	6 449 (1.4)	1 (ref.)	1 (ref.)
Renal insufficiency	231 (81.1)	47 (16.5)	7 (2.5)	0.6 (0.5–0.8)	1.7 (0.8–3.5)

Notes: nsNSAID: non-selective non-steroidal anti-inflammatory drug; NSAID: non-steroidal anti-inflammatory drug; MSK: musculoskeletal; CV: cardiovascular; MI: myocardial infarction; AP: angina pectoris; TIA: transient ischaemic attack; PAD: peripheral arterial disease; UGI: upper gastrointestinal. ¹Row percentage.

Influence of UGI risk

Table III shows the odds of coxib and nsNSAID prescription versus no NSAID prescription in patients with a high or moderate CV risk versus patients with a low CV risk, stratified per UGI risk group. Within each UGI risk group, differences in prescription of nsNSAIDs and coxibs were found when comparing patients with a high or moderate CV risk with patients with a low CV risk. Notably for coxib prescription the direction of this difference varied depending on the UGI risk group. When

adjusted for age, gender, previous NSAID prescription, the type of MSK complaint diagnosed, and the presence of renal insufficiency, these differences diminished in magnitude but the same pattern still remained.

Prescription of nsNSAIDs and coxibs over time

Figure 1 shows the prescription of nsNSAIDs and coxibs over time. The prescription of coxibs initially increased over time in both high and low CV risk

Table III. Prescription of coxibs and nsNSAIDs versus no NSAID in moderate and high CV risk patients versus low CV risk patients per UGI risk group.

UGI risk group	CV risk group	Number of patients	No NSAID n (%)	nsNSAID n (%)	Coxib n (%)	OR (95% CI)		Adj. OR (95% CI) ²	
						nsNSAID vs. no NSAID	coxib vs. no NSAID	nsNSAID vs. no NSAID	coxib vs. no NSAID
Low	Low	305 168	226 617 (74.3)	75 915 (24.9)	2 636 (0.9)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Moderate	22 003	15 842 (72.0)	5 836 (26.5)	325 (1.5)	1.1 (1.1–1.1)	1.7 (1.5–1.9)	0.9 (0.9–0.9)	1.1 (1.0–1.2)
	High	8 385	6 246 (74.5)	2 002 (23.9)	137 (1.6)	1.0 (0.9–1.0)	1.9 (1.6–2.3)	0.8 (0.8–0.8)	1.3 (1.1–1.5)
Moderate	Low	34 692	24 776 (71.4)	9 164 (26.4)	752 (2.2)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Moderate	21 058	14 945 (71.0)	5 708 (27.1)	405 (1.9)	1.0 (1.0–1.1)	0.9 (0.8–1.0)	1.0 (1.0–1.1)	0.9 (0.8–1.2)
	High	8 093	6 003 (74.2)	1 920 (23.7)	170 (2.1)	0.9 (0.8–0.9)	1.0 (0.8–1.1)	0.8 (0.8–0.9)	1.0 (0.8–1.2)
High	Low	25 674	19 365 (75.4)	5 536 (21.6)	773 (3.0)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Moderate	24 123	18 183 (75.4)	5 308 (22.0)	632 (2.6)	1.0 (1.0–1.1)	0.9 (0.8–1.0)	1.0 (1.0–1.1)	0.9 (0.8–1.0)
	High	25 005	20 055 (80.2)	4 324 (17.3)	626 (2.5)	0.8 (0.7–0.8)	0.8 (0.7–0.9)	0.8 (0.7–0.8)	0.8 (0.7–0.9)

Notes: nsNSAID: non-selective non-steroidal anti-inflammatory drug; NSAID: non-steroidal anti-inflammatory drug; CV: cardiovascular; UGI: upper gastrointestinal. ¹Row percentage. ²Adjusted for age, gender, prescription of NSAIDs in six months prior, type of MSK complaint, and presence of renal insufficiency.

patients, until 2004, after which a sharp decrease is observed. During the peak year of 2004, the odds of prescription of coxibs in high CV risk patients was around three times higher than in 2000 and in 2005 (OR 2.9, 95% CI 2.2–3.7 and OR 3.4, 95% CI 2.5–4.6 for 2004 versus respectively 2000 and 2005, not shown in figure).

The odds of coxib prescription were significantly higher in patients at high CV risk than in patients at low CV risk (Table IV), not only between 2000 and 2004 but also between 2005 and 2010. The odds of

nsNSAID prescription remained significantly lower in patients at high CV risk than in patients at low CV risk in both time periods. In a sensitivity analysis in which prescriptions of naproxen and prescriptions with a PDD smaller than half the DDD were excluded, the odds of prescription of an nsNSAID or coxib versus no NSAID, in patients with a high CV risk versus patients with a low CV risk, were almost the same as that of all nsNSAIDs or coxibs versus no NSAIDs in both time periods (OR 0.8, 95% CI 0.8–0.8 and OR 0.7, 95% CI 0.7–0.8, for

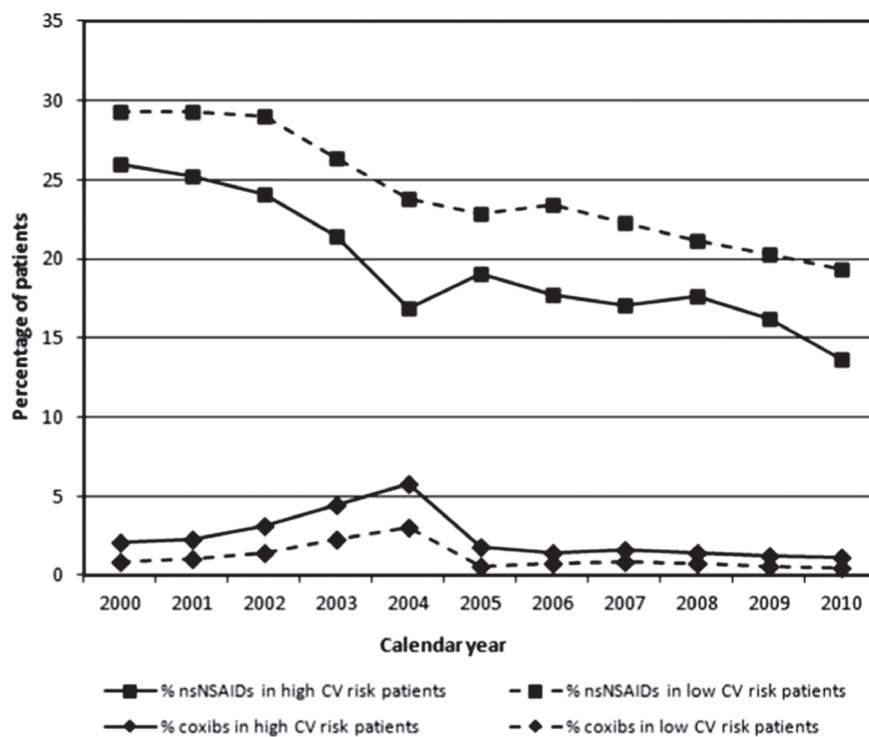


Figure 1. Percentage of patients with a high CV risk and with a low CV risk prescribed an nsNSAID or a coxib per year.

Table IV. Prescription of coxibs and nsNSAIDs versus no NSAID in moderate and high CV risk patients versus low CV risk patients per time period.

Time period	CV risk group	Number of patients	No NSAID n (%) ¹	nsNSAID n (%) ¹	Coxib n (%) ¹	Adj. OR (95% CI) ²	
						nsNSAID vs. no NSAID	coxib vs. no NSAID
2000–2004	Low	181 443	127 912 (70.5)	50 670 (27.9)	2 861 (1.6)	1 (ref.)	1 (ref.)
	Moderate	27 421	18 939 (69.1)	7 703 (28.1)	779 (2.8)	1.0 (1.0–1.1)	1.9 (1.7–2.1)
	High	18 574	13 619 (73.3)	4 349 (23.4)	606 (3.3)	0.8 (0.8–0.8)	2.0 (1.8–2.2)
2005–2010	Low	184 091	142 846 (77.6)	39 945 (21.7)	1 300 (0.7)	1 (ref.)	1 (ref.)
	Moderate	39 763	30 031 (75.5)	9 149 (23.0)	583 (1.5)	1.1 (1.1–1.1)	2.3 (1.9–2.4)
	High	22 909	18 685 (81.6)	3 897 (17.0)	327 (1.4)	0.8 (0.7–0.8)	1.9 (1.7–2.2)

Notes: CV: cardiovascular; NSAID: non-steroidal anti-inflammatory drug; nsNSAID: non-selective non-steroidal anti-inflammatory drug. ¹Row percentage. ²Adjusted for year of MSK complaint episode within the time period.

nsNSAID versus no NSAID in 2000–2004 and 2005–2010 respectively; OR 2.0, 95% CI 1.8–2.2 and OR 1.9, 95% 1.7–2.2 for coxib versus no NSAID in 2000–2004 and 2005–2010 respectively, not shown in table).

Discussion

Statement of principal findings

In this study, we examined the prescription of NSAIDs in the treatment of MSK complaints by GPs over the course of the last decade, in which evidence emerged regarding the CV risks of these drugs. We found that one-quarter of all patients presenting with a MSK complaint were treated with an NSAID. Prescription varied widely depending on the type of MSK complaint diagnosed. Coxibs gained in popularity during the first five years of marketing in the Netherlands, with prescription among high CV risk patients in 2004 almost three times higher than in 2000. After rofecoxib was removed from the market, a decrease in coxib prescription was observed. The decrease in coxib prescription observed after 2004 occurred not only in patients with a high CV risk, but equally in patients with a low CV risk, even after their use was contraindicated in these patients by the European Medicines Agency in 2005 [14]. Conversely, nsNSAIDs were prescribed less frequently in patients with a high CV risk than in patients with a low CV risk throughout the study period. These observed differences in prescription between CV risk groups can be partly explained by the overlap between CV risk and UGI risk. When stratified for UGI risk, the odds of both nsNSAID and coxib prescription decreased with increasing CV risk in patients at moderate or high UGI risk. Interestingly, however, for coxibs the opposite pattern was observed for patients with a low UGI risk. When corrected for other predictors, within the low

UGI group coxibs were still prescribed more frequently in those with a high CV risk than in those with a low CV risk, suggesting that other factors play a role in GPs' decision to prescribe these drugs.

Strengths and weaknesses of the study

The strength of this study is that it was conducted in a database containing a large number of patients reflecting the Dutch general population. Nonetheless, some limitations should be considered when reviewing the results. First, only patients presenting with an ICPC-coded MSK complaint were included in the cohort. As some GPs may apply the ICPC coding more diligently than others, this may have led to an underestimation or overestimation of NSAID treatment, if the prescribing behaviour of GPs is in any way related to their tendency to apply the ICPC coding. Second, we did not have any information on over-the-counter (OTC) use of analgesics. Although coxibs are not available without prescription in the Netherlands, nsNSAIDs are freely available. While this is important, our objective in this study was to determine the association between the cardiovascular risk profile of a patient and NSAID prescription by the GP.

Strengths and weaknesses in relation to other studies

Various studies examining changes in NSAID prescription in primary care over the past decade have been published [31–34]. However, few large-scale studies have focused specifically on the influence of CV risk on the prescription of NSAIDs by GPs, which was the aim of the present study. One prior study did investigate this in the primary care population as we did, but it only reported on the years 2000 to 2004, before evidence emerged of the CV risk of NSAIDs [35]. Other studies which have reported on CV risk and the use of NSAIDs both before and after

rofecoxib withdrawal in 2004 [36,37] were not population-based. In addition, in these studies the CV risk profile of the patients was determined based on surrogate pharmacy markers. The strength of our population-based study lies in the fact that we were able to identify all relevant risk factors by conducting free text searches, assessing ICPC-codes and prescriptions of medication, using GP medical records which form a complete record of each patient's medical data.

Meaning of the study

Although international guidelines have provided recommendations on NSAID prescription in patients with CV risk factors [19,20], as of yet no national Dutch guideline has been published specifically on this topic. The most recent Dutch guideline specifically on NSAID prescription was published in 2003 [25], at which point in time little was known about the CV risks associated with NSAID use. Over time, prescription of NSAIDs has decreased in all risk groups, which might relate to awareness of GPs regarding risks associated with NSAIDs. Nonetheless, overall one in five patients with a high CV risk presenting with a new MSK complaint received an NSAID. It appears that GPs do not fully consider the CV risks associated with NSAID use when prescribing NSAIDs in these patients, indicating that there is still room for improvement.

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Declaration of interest

Vera Valkhoff conducted research for AstraZeneca in the past as an employee of the Erasmus MC University Medical Center. Miriam Sturkenboom coordinates a research group that occasionally performs research for pharmaceutical industries. None of the grants was related to the submitted work. The other authors declare no other relationships or activities that could appear to have influenced the submitted work. The authors alone are responsible for the content and writing of the paper.

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